Cardiac Fibroblasts Adopt Osteogenic Fates and Can Be Targeted to Attenuate Pathological Heart Calcification.

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Public Summary:
Calcification of tissues occurs with age, injury and many common diseases such as diabetes and chronic kidney disease. Calcification of tissues is thought to be cell mediated dynamic process analogous to bone formation in the skeleton where bone forming cells are recruited to the affected region and lead to mineralization of the matrix. However the heart does not contain bone forming cells and the origin of these cells that causes calcification remained a mystery. Here we show that fibroblasts of the heart behave like stem cells and adopt bone forming cell like characteristics and lay down abnormal calcium deposits. We show that a key molecule ENPP1 mediates this process and inhibition of ENPP1 significantly attenuates abnormal cardiac calcification. Heart calcification is an incurable disease and there are no therapies currently available.These observations offer for the first time a novel therapeutic target for treating ectopic calcification of the heart.

Scientific Abstract:
Mammalian tissues calcify with age and injury. Analogous to bone formation, osteogenic cells are thought to be recruited to the affected tissue and induce mineralization. In the heart, calcification of cardiac muscle leads to conduction system disturbances and is one of the most common pathologies underlying heart blocks. However the cell identity and mechanisms contributing to pathological heart muscle calcification remain unknown. Using lineage tracing, murine models of heart calcification and in vivo transplantation assays, we show that cardiac fibroblasts (CFs) adopt an osteoblast cell-like fate and contribute directly to heart muscle calcification. Small-molecule inhibition of ENPP1, an enzyme that is induced upon injury and regulates bone mineralization, significantly attenuated cardiac calcification. Inhibitors of bone mineralization completely prevented ectopic cardiac calcification and improved post injury heart function. Taken together, these findings highlight the plasticity of fibroblasts in contributing to ectopic calcification and identify pharmacological targets for therapeutic development.